American Journal of Pharmacy

AND THE SCIENCES
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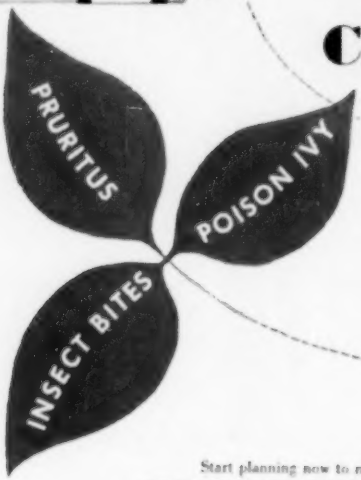

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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EDITORIAL

PROFESSIONAL CONTACT OR SELF-SERVICE?

AT a recent meeting, attended by a large number of retail pharmacists, a top sales executive of one of our leading pharmaceutical companies addressed the group. He spoke in glowing terms of a new approach being used to boost drug sales and urged all pharmacists present to consider seriously the introduction of this new technic of selling in their own stores. He recommended a long open counter in the center of the store on which every product that could be sold without a prescription was to be placed so that customers might simply help themselves and then pay a clerk or cashier—nothing more or less than the technic used in today's supermarkets.

Were it not for the fact that we were the guests of the company in question such a suggestion would have led us to an immediate public denouncement of this plan which, if it becomes widely accepted, not only will be inimical to public health and safety but also seriously impair the professional and economic status of pharmacy.

It is unfortunate that some few sales executives ofttimes evaluate a sales promotion plan only in terms of immediate results and fail to consider its long range effects. We shall not attempt to refute the claim that such a plan will increase sales, for it has been amply demonstrated that display and easy accessibility cause people to buy more merchandise, regardless of the kind of products displayed. Our concern is with the more intangible and insidious effects of such a program.

In the first place we must insist that the selling of drug products cannot be compared with the selling of foods, cosmetics toys, magazines and the like. A desire to purchase a given drug is not necessarily all that is required in order properly to consummate the sale. In many cases a customer must be given certain advice concerning the use of the drug and in some instances even discouraged from buying it altogether. It is true that products for sale to the public are required to carry adequate directions for use including all warning statements, but it is quite well established that few people read the label and many of those who do fail to appreciate its full significance. There is practically no drug which is so safe and well known that its unrestricted sale by untrained personnel is entirely without hazard. It is, furthermore, far more conducive to public welfare to have all drugs sold at least under the supervision

of a registered pharmacist. Let us take, for example, one of our most common and safest drugs, aspirin. Who but the pharmacist knows:

(a) that its use may cause severe gastritis;
(b) that persons have died from taking as little as 15 grains;
(c) that it may be used to commit suicide;
(d) that long continued use may depress blood prothrombin and cause spontaneous internal hemorrhages; and
(e) that it is unstable in a moist atmosphere and the degree of deterioration is easily determined with a ferric chloride colorimetric test.

"Yes", someone will say, "but does the pharmacist utilize this knowledge when he sells aspirin?" The answer is that he does when, according to his professional judgment, a given sale requires it.

The situation is exactly parallel to that which occurs when a man with a cold visits a physician. In 99 cases out of 100 no skill or professional knowledge is required to diagnose or prescribe for the patient, but are we therefore to suggest that persons with a bad cold do not require a physician's attention?

Another very great hazard in the self-service type of operation is that drugs may easily get into the hands of children or irresponsible persons. If all one must do is to pick up a package it is impossible to prevent this from happening. We insist that boric acid and a loaf of bread are in totally different categories from the standpoint of potential harm.

Our final objection to the self-service plan is that, once adopted by pharmacists generally, it will destroy all validity of pharmacy's argument that drugs should be sold only in drug stores. A supermarket in a drug store is still a super market and if we pharmacists endorse the plan then we shall be telling the public, our legislators and the world that the supervised sale of drugs is totally unnecessary. We may then say farewell to the restrictive legislation in many states limiting drugs to drug stores; only prescription items will belong exclusively to pharmacy. If we pharmacists are so foolish as to ignore our professional status and responsibilities, if we choose the easy path to better sales, then we shall indeed sell our birth right for a mess of potage. We shall live to regret the professional and economic morass into which we fell blindly and headlong, like sheep following an unwise leader over a precipice.

L. F. Tice

THE NEW DRUGS IN THE U. S. P. XIV

(Part II)

By L. F. Tice *

Pentaquine Phosphate
Pentaquine Phosphate Tablets

Chemically, this is the phosphate of 8-(5-isopropylamino-amylamino)-6-methoxy quinoline. It is a yellow, crystalline, odorless powder with a bitter taste.

Pentaquine and the closely related isopentaquine were developed as the result of the intensive research on antimalarials during the war. The former was known as SN 13,276 and the latter as SN 13,274. Pentaquine is not used as a suppressive but as a drug for the radical cure of benign tertian (vivax) malaria. It is chemically related to pamaquine, but it is less toxic and more efficient. Just as in the case of pamaquine it must not be given in conjunction with quinacrine. Quinacrine raises its blood concentration and thereby increases its toxicity.

Pentaquine Phosphate is generally given with quinine, and the dosage schedule for ambulant patients is 13.3 mg. (10 mg. base) plus 300 mg. of quinine sulfate 3 times a day for 14 days. Twice this dose of both drugs may be used for patients who are hospitalized when daily observation for toxic effects is possible. These toxic effects are methemoglobinemia and occasionally intravascular hemolysis.

Pentaquine in conjunction with quinine is claimed to reduce the relapse rate of vivax malaria from 98 to 25 per cent following one course of therapy and to only 2 per cent following a second course of therapy. It is available under its official title in tablet form from Abbott Laboratories. This company also supplies it with quinine in tablet form each containing 10 mg. of pentaquine base (as phosphate) and 300 mg. of quinine sulfate.

Pentobarbital Sodium Injection

The official definition of this product is simply a sterile solution of pentobarbital sodium in a suitable solvent. Since pentobarbital sodium is unstable in aqueous solution, water may not be used to prepare this injection if it is to be kept any length of time. Aqueous

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solutions are also decomposed when sterilized by heat. Commercial products which are available are prepared with either a water-alcohol solvent or propylene glycol containing 2 per cent benzyl alcohol, as the solvent. The usual concentration of these products is 0.162 Gm. per cc. or 0.05 Gm. per cc.

The injection is used intramuscularly in those cases where oral administration is impossible or undesirable.

Pentobarbital Sodium, Sterile

Pentobarbital Sodium was recognized in the U. S. P. XIII as it is in the new Pharmacopeia for oral use. Sterile Pentobarbital Sodium is usually packaged in dry ampuls to maintain its sterility. Prior to use by intravenous injection it is dissolved in water for injection with aseptic procedure. The usual dose is 100 to 150 mg., and a dose of 500 mg. at one time must never be exceeded. It is used intravenously where a very rapid effect is desired. Such is the case in convulsive seizures due to tetanus, rabies, eclampsia, poisoning by strychnine, cocaine, etc.

Pentobarbital Sodium is available under its official title from a number of sources, and it is sold by Abbott Laboratories as *Nembutal Sodium.*

Pentylenetetrazol
Pentylenetetrazol Injection

This is also known as pentamethylenetetrazol. It is a white, crystalline, odorless substance with a slightly pungent, bitter taste. It is soluble in water forming a neutral solution. Pentylenetetrazol is used for its powerful stimulant effect on the mid-brain and the medullary centers. It is employed in the treatment of barbiturate poisoning, and it is believed to be superior to picrotoxin for this purpose. It is also used in the shock therapy of mental disorders in which it is judged safer than insulin. The use of curare to soften the convulsions which it produces is growing in popularity.

Pentylenetetrazol has been recommended as a cardiac and respiratory stimulant, but its value in these fields is not clearly established. It is given orally and by parenteral injection. The usual dosage range is 100 to 300 mg. repeated as necessary. In the treatment of barbiturate poisoning very large doses are given intravenously in accordance with the needs of the patient. Since its action when given intravenously is both rapid and of brief duration, the dosage level can be controlled by following its effect on the patient.

Pentylenetetrazol is available as Pentamethylenetetrazol and also under the proprietary name of *Metrazol* from the Bilhuber-Knoll Corp.

Pertussis Vaccine

This is a sterile suspension in isotonic sodium chloride of killed pertussis bacilli (*Hemophilus pertussis*). The strain used is selected for high antigenic efficiency. Each cc. contains at least 10,000 million pertussis organisms. It is a turbid liquid, nearly odorless or having a faint odor due to the presence of a preservative.

Pertussis Vaccine is used in the active immunization of children against whooping cough. Although many cases still develop following its use, they are usually much less severe, and the death rate is greatly reduced. The total dose given must be at least 60,000 million organisms divided into not less than 3 injections spaced at 3 to 4 week intervals and given hypodermically. Still larger doses are probably desirable. The age at which pertussis vaccine is usually given is 6 months. A booster dose is then given when the child enters school or when he is exposed to the disease.

Pertussis Vaccine, Alum Precipitated

This is essentially the same material as pertussis vaccine, except the organisms are precipitated with alum and resuspended. Each cc. contains at least 10,000 million organisms. The immunizing dose of the alum precipitated vaccine is not less than 30,000 million bacteria divided into not less than 3 injections spaced at 4 to 6 week intervals.

Phenobarbital Sodium Injection

Phenobarbital Sodium Injection is a sterile solution of phenobarbital sodium in a suitable solvent. Just as described under Pentobarbital Sodium, water is not a suitable solvent for the sodium derivatives of the barbiturates when the solution is to be kept for a period of time or sterilized. The solvent generally employed to make Phenobarbital Sodium Injection is propylene glycol. A small amount of benzyl alcohol is frequently added and some water may also be present. Phenobarbital Sodium is, of course, a long-acting barbiturate, and its indications and uses are somewhat different than those of the short-acting Pentobarbital Sodium.

The products which are available contain from 0.12 Gm. to 0.30 Gm. per cc., and the dose ranges from 30 to 300 mg. The injection is given intramuscularly or subcutaneously but not intravenously.

A number of companies supply Phenobarbital Sodium in a solution form which conforms with the requirements of the official monograph for the Injection. The proprietary name, *Solution Luminal Sodium in Propylene Glycol,* is used by Winthrop-Stearns, Inc.

Phenobarbital Sodium, Sterile

This is usually packaged in a dry ampul and a solution prepared with water for injection by aseptic procedure just before administering the drug. It is given subcutaneously, and the dose is from 30 to 300 mg. given usually as a 20% solution.

Phenylephrine Hydrochloride
Phenylephrine Hydrochloride Injection
Phenylephrine Hydrochloride Solution

The chemical name of this substance is *l*-1-(m-hyroxyphenyl)-2-methylamino-ethanol hydrochloride. It is a white, or nearly white, crystalline, odorless substance. It is soluble in water giving a solution which is acid to litmus and having a bitter taste.

This substance is a sympathomimetic amine having a vasopressor action when injected or taken orally. When applied locally to mucous membranes, it acts as a vasoconstrictor and reduces swelling and congestion.

Phenylephrine Hydrochloride is often combined with a local anesthetic to be used by injection, in much the same manner and for the same purpose as is epinephrine hydrochloride. It is injected to combat acute hypotension due to peripheral circulatory collapse or following spinal anesthesia. Solutions placed in the eye are mydriatic, and the drug is sometimes used in combination with cycloplegics. Strong solutions are used in the eye to prevent or relieve posterior synechiae. When given by injection the dose is 1 to 10 mg., the initial dose not exceeding 5 mg. If given by the intravenous route only one-tenth this amount should be administered. For use as a vasoconstricting agent on the nasal mucosa a 0.25-0.50 per cent isotonic solution is employed; as a mydriatic 1 or 2 drops of a 1 per cent or a 2½ per cent solution is used; for the freeing of posterior synechiae 1 drop of a 10 per cent solution is used.

Phenylephrine Hydrochloride is available in a wide variety of products sold by Winthrop-Stearns under the proprietary name of *Neo-Synephrine Hydrochloride.*

Phthalylsulfathiazole
Phthalylsulfathiazole Tablets

This is a condensation product of phthalic anhydride and sulfathiazole, and chemically it is 2-(N^4-phthalylsulfanilamido) thiazole. It is a white or faintly yellowish white, crystalline powder which is practically insoluble in water.

Phthalylsulfathiazole is given orally in tablet form for the treatment of intestinal infections caused by sulfonamide susceptible organisms. About 95 per cent of that given orally passes through the gastrointestinal tract unabsorbed. It is useful in the treatment of inflammations of the intestinal tract and particularly for the presurgical treatment of patients who are to be subjected to surgery involving the small intestine or colon. While it does not itself cure ulceratis colitis or regional ileitis, its use often provides considerable improvement in patients with these conditions. It is given at a dosage level dependent upon the nature of the condition for which it is used. Prior to surgery, an initial dose of 125 mg. per kilogram is given followed by the same amount each day in divided doses for 3 to 5 days. In other conditions the adult oral dose is 4 to 6 Gm. daily in divided doses. For ulcerative colitis where therapy must often be used for many weeks much smaller doses of the drug may be adequate. Such small doses should be used if consistent with proper response by the patient.

Phthalylsulfathiazole is sold by Sharp & Dohme, Inc. as *Sulfathalidine*, and it is available as 0.5 Gm. tablets or in suspension as *Cremothalidine* which contains 6 Gm. in each 30 cc.

Pilocarpine Hydrochloride

This was official in the N. F. VIII and the nitrate was recognized in the U. S. P. XIII. Both pilocarpine salts are now in the U. S. P. XIV. Their uses are quite identical and well known. The reason for the inclusion of 2 pilocarpine salts in the Pharmacopeia does not seem well established.

Piperocaine Hydrochloride
Piperocaine Hydrochloride Injection

The chemical name of this substance is 3-benzoxy-1-(2-methylpiperidino)-propane hydrochloride. It is a white crystalline powder which when placed upon the tongue produces a sense of numbness. Piperocaine Hydrochloride is a local anesthetic which is

used topically, for infiltration anesthesia, as a spinal anesthetic and for caudal anesthesia. Topically, it is used in strengths varying from 0.25 per cent to 10 per cent depending upon the area treated. Thus for instillation into body cavities as low as 0.25 per cent is used; for the nose and throat 2 to 4 per cent solutions are employed, and in the eye 2 to 4 per cent solutions are used depending upon the degree of anesthesia desired. For infiltration anesthesia it is used in from 0.25 to 1.0 per cent solutions usually combined with epinephrine. In spinal anesthesia different strength solutions, ranging from 1.5 per cent to 5 per cent, are used depending upon the technic employed and the dose desired. Piperocaine Hydrochloride Injection is available from Eli Lilly and Co. in various strengths intended for different technics of administration. It is sold under the proprietary name of *Metycaine*.

Polyethylene Glycol 400

This is a condensation polymer of ethylene oxide and water represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$ where n varies from 7 to 9. It is a clear, colorless or practically colorless, viscous liquid having a slight characteristic odor. It is miscible with water, alcohol, acetone and the glycols.

This substance is recognized in the Pharmacopeia as an ingredient of Polyethylene Glycol Ointment.

Polyethylene Glycol 4000

This, too, is a condensation polymer of ethylene oxide and water in which the n value in the formula given above varies from 70 to 85. It is a pale creamy-white, waxy solid resembling paraffin in appearance and texture. It is practically odorless and tasteless, and it is soluble in water. This is known commercially as *Carbowax 4000* and is sold by Carbide & Carbon Chemicals Corp. It is used to prepare Polyethylene Glycol Ointment.

Polyethylene Glycol Ointment

This is composed of equal parts by weight of polyethylene glycol 400 and 4000, and it is prepared by fusion. If a softer product is desired, as much as 20 per cent of the polyethylene glycol 4000 may be replaced with the 400.

Polyethylene Glycol Ointment is commonly known as a *Carbowax* base. It is completely non-irritating, inert, and water soluble. Such a base has gained considerable favor as an ointment vehicle

and replaces the older fatty or hydrocarbon bases. A number of commercial ointments are prepared with bases which closely resemble this new official base.

Polysorbate 80

This is a complex mixture of polyoxyethylene ethers of a mixture of partial oleic acid esters of various sorbitol anhydrides. It is a lemon to amber colored, oily liquid having a faint, characteristic odor and a warm, somewhat bitter taste. It is soluble in water, alcohol and fixed oils.

Polysorbate 80 is better known under its proprietary name, *Tween 80*, as supplied by the Atlas Powder Co. and sold by various outlets. It belongs to that very important class of emulsifying and dispersing agents known as the non-ionic agents. These are so named since they carry neither a positive nor a negative charge. The *Tweens* possess very unusual properties as surface-active agents and they, together with a related group, the *Spans*, are finding many applications in pharmacy and medicine. Polysorbate 80 is recognized in the Pharmacopeia as a pharmaceutic necessity for use in preparing benzyl benzoate chlorophenothane lotion. It serves as the emulsifying agent in this preparation.

Potassium Nitrate

This salt has been official for many years, and it was recognized in the N. F. VIII. It has been included in the U. S. P. XIV. Its therapeutic use is similar to that of potassium chloride which is given to raise the potassium level of the blood in various neuromuscular diseases and in conditions associated with potassium depletion.

Procaine Hydrochloride and Epinephrine Injection
Procaine Hydrochloride Injection

Procaine Hydrochloride Ampuls were official in the N. F. VIII. The Injection, as recognized in the U. S. P. XIV, has essentially the same monograph.

Procaine Hydrochloride and Epinephrine Injection is an identical product except that it contains epinephrine usually in a concentration of 1-2500. This product is particularly useful in infiltration anesthesia since the epinephrine by its vasoconstricting action tends to prolong the effect.

The injection with and without epinephrine is supplied by numerous companies. It is also sold under the proprietary name *Novocain* in many dosage forms by Winthrop-Stearns.

Procaine Hydrochloride, Sterile

This is a sterile procaine hydrochloride usually packaged in a dry ampul. It is specifically intended for use in spinal anesthesia. For this purpose the sterile product is dissolved in water for injection by strictly aseptic procedure. Concentrations not exceeding 5 per cent and a total dose not exceeding 200 mg. are employed. Spinal anesthesia is, of course, a procedure requiring considerable skill and technic, and it should not be attempted except by those well-trained in this field.

Many new uses for procaine hydrochloride have been reported such as its intravenous use to relieve pain in arthritis and in carbon monoxide poisoning.

Propylene Glycol

This solvent was official in the N. F. VIII, and it is now recognized in the U. S. P. XIV. It was originally used largely as a substitute for glycerin, but its use has been expanded, and for some purposes it is superior to glycerin. It is relatively non-toxic, and it is permitted in both oral and injection products. The Pharmacopeia recognizes it as a pharmaceutic necessity since it is used in some official preparations.

Propylthiouracil
Propylthiouracil Tablets

This chemically is 6-*n*-propyl-2-thiouracil and is a white, crystalline powder having much of the appearance of starch and a bitter taste. It is only slightly soluble in water. Propylthiouracil is an antithyroid drug which interferes with the formation of thyroxin by the thyroid gland. It is used in the treatment of hyperthyroidism, thyrotoxicosis and thyroiditis. The drug does not in any way interfere with the thyroxin already formed by the thyroid, and thus its clinical effect may not be evidenced for several days or even longer. Propylthiouracil is recommeded particularly in those cases where surgery is contraindicated and in the preparation of patients for surgery. In the latter instance propylthiouracil should be supplemented with iodides the last two or three weeks before surgery. Unlike iodide therapy in thyrotoxicosis, the effectiveness of propylthiouracil is sustained over a long period if its use is continued.

Although the toxicity of propylthiouracil is much less than the older drug thiouracil, there is still some danger attending its use. The most serious toxic manifestation is granulocytopenia, and less

severe effects include leukopenia, drug rash and fever. Patients should be cautioned to report back to their physician immediately if sore throat, coryza or fever develop. The dose of propylthiouracil is 50 mg. 3 times daily in severe cases and 50 mg. 2 times daily in less severe cases. The drug is available from a number of sources.

Raspberry Juice
Raspberry Syrup

The Juice is recognized as an ingredient of the Syrup. Both were official in the N. F. VIII and are among the several such vehicles recognized in the U. S. P. XIV.

Rose Water Ointment, Petrolatum

Petrolatum Rose Water Ointment differs from rose water ointment only that in the former liquid petrolatum is substituted for the expressed almond oil or persic oil. The resulting product does not easily develop rancidity on long standing, and it is similar to many of the cosmetic "cold creams" on the market.

Salicylic Acid Plaster

This preparation is a uniform mixture of salicylic acid in a suitable base spread on paper, cotton cloth or other suitable backing material. The plaster is used for the well-known keratoplastic effect of salicylic acid on hardened, keratinized epidermal tissue. The so-called "corn plasters" are typical of this kind of product.

Serum, Anti-A Blood Grouping
Serum, Anti-B Blood Grouping

These serums are derived from high titered serums of persons, with or without stimulation by the injection of group specific red cells or substances, or by similar treatment of lower animals. Anti-A Blood Grouping Serum agglutinates human red cells containing A agglutinogens; i. e., groups A and AB (sub-groups A_1, A_2, A_3, A_1B, and A_2B). Anti-B Blood Grouping Serum agglutinates human red cells containing B agglutinogens; i.e., groups B and AB (sub-groups A_1B and A_2B).

These serums are used in the well-known procedure for blood typing. Blood type is prerequisite knowledge concerning both donor and recipient in blood transfusion if serious complications are to be avoided.

Anti-A and Anti-B Blood Grouping Serums are available from Lederle Laboratories, Cutter Laboratories and the Wm. S. Merrell Co.

Serum, Anti-Rh Typing

Anti-Rh Typing Serum is derived from the blood of persons who have developed specific Rh antibodies. It is used as a diagnostic aid to determine whether an individual is Rh positive or Rh negative. Highly specialized serums are also available to determine, more precisely, the exact Rh type of an individual, there being several types known. The test is an agglutination test performed with the patient's blood and the Anti-Rh Typing Serum. Each product must be used in accordance with the highly specific technic given for that product.

A knowledge of Rh type is of very great importance in selection of bood for transfusion, in prediction of transfusion reactions, and in diagnosis of the cause of erythroblastotic infants. It is also of value in a number of other directions, including the compilation of medico-legal data.

Anti-Rh Typing Serum is available from the Ortho Pharmaceutical Corp. and from Lederle Laboratories.

Silver Nitrate Ophthalmic Solution

This is a buffered solution of silver nitrate containing in each 100 cc. not less than 0.95 Gm. and not more than 1.05 Gm. of $AgNO_3$. Its pH is between 5 and 6.

Silver Nitrate Ophthalmic Solution is usually packaged in special wax capsules each containing about 5 drops of the solution. It is intended for use in ophthalmia neonatorum, 2 drops being placed in each eye, and the lids manipulated to bring the solution into contact with all portions of the conjunctival sac. Each capsule contains sufficient solution to treat both eyes.

Sodium Bisulfite

This is recognized solely for its use as a pharmaceutic necessity. Its antoxidant effect makes it of value in the preparation of a number of solutions containing substances which are readily oxidized.

Sodium Iodomethamate
Sodium Iodomethamate Injection

The chemical name of this substance is disodium 1-methyl-3,5-diiodo-4-pyridone-2,6-dicarboxylate. It is a white, odorless powder which is quite soluble in water. It is used as a contrast medium in both intravenous urography and retrograde pyelography.

For intravenous urography 20 cc. of a solution containing 0.75 Gm. per cc. are injected into the cubital vein. Roentgenograms are then taken at intervals of 5, 15 and 30 minutes. In the event of poor kidney function a much longer period may be required before a satisfactory plate is obtained. The dosage for children is 10 cc., or less, of the above solution depending on age.

Systemic reactions following the use of the drug are usually mild, but in a few cases there may be some pain in the arm and shoulder.

For retrograde pyelography a 20 per cent solution is employed. This is made by the appropriate dilution of the stronger solutions which are sold commercially.

This drug is supplied by the Schering Corp. under the proprietary name of *Neo-Iopax*. It is available as a 75 per cent solution in 10 and 20 cc. ampuls and as a 50 per cent solution in 10, 20 and 30 cc. ampuls.

Sponge, Absorbable Gelatin

This is defined, officially, as a sterile, absorbable, water-insoluble gelatin-base sponge. It is made from a non-pyrogenic, non-antigenic gelatin matrix. The gelatin is partially denatured so that it is insoluble in water but slowly soluble in tissue fluid and digestible by pepsin.

Absorbable Gelatin Sponge is used as a hemostatic agent. For such use it is saturated with sterile normal saline solution or a thrombin solution and applied to the area where hemostasis is desired and held there for 10-15 seconds with gentle pressure. It may be left in the body since it is slowly absorbed with only a minimum of scar tissue development.

It is available from The Upjohn Co. as *Gelfoam, No. 12, Sterile* which contains 4 sponges each 20 x 60 mm. (12 $cm.^2$) x 7 mm., *Gelfoam, No. 100, Sterile* which contains 6 sponges each 80 x 125 mm. (100 $cm.^2$) x 10 mm. and as *Gelfoam Dental Packs*.

Absorbable Gelatin Sponge is also used to trap cells from an accessible body area suspected of being cancerous. The sponge is then fixed in a formaldehyde solution. It may then be sectioned and stained by the Papanicalaou technic and examined microscopically for cells characteristic of a malignant lesion.

A special package for this purpose is supplied by The Upjohn Co. as *Gelfoam Tumor Diagnosis Kit*.

Stibophen
Stibophen Injection

This is sodium antimony III bis-catechol-2,4-disulfonate heptahydrate. It contains 13.6 per cent of trivalent antimony. This drug was official in the N. F. VIII. It is sold by Winthrop-Stearns under the proprietary name, *Fuadin*, in 3.5 and 5cc. ampuls each cc. containing 63 mg. of the drug. It is useful in both granuloma inguinale and in schistosomiasis.

Streptomycin

This consists of the several antibiotic substances produced by the growth of *Streptomyces griseus* or each of the same substances produced by any other means. It is available as the hydrochloride, as the hydrochloride double salt with calcium chloride, as the phosphate or as the sulfate.

It is usually a white to slightly colored (pink or brown) granular substance or powder.

Streptomycin is a very well-known antibiotic, and no effort will be made here to include all the important data concerning its properties and uses. It is particularly useful against infections caused by gram negative organisms; thus it has a bacterial spectrum quite different from that of penicillin. Since it is not absorbed from the intestinal tract, it may be given orally only for intestinal infections. For systemic infections it is usually given by intramuscular injection in a dosage of from 1 to 4 Gm. daily depending upon the nature of the infection and the susceptibility of the organism. The solution injected should contain from 100-200 mg. per cc. The intravenous and subcutaneous route are also employed at times.

Streptomycin differs from penicillin in a number of important respects other than in antibacterial spectrum. The invading organisms rapidly acquire tolerance to the drug if inadequate dosage is given. The drug is also somewhat toxic, particularly to the eighth cranial nerve, often causing vertigo and deafness. A caloric stimulation test is often used to detect early signs of neurotoxicity.

Streptomycin is available in a number of forms from a number of companies.

Sulfur Dioxide

This gas, like nitrogen, is recognized solely as a pharmaceutic necessity since it is used in some official products.

Suramin Sodium, Sterile

Suramin Sodium was official in the U. S. P. XIII. It was not listed for inclusion in the U. S. P. XIV since it is so rarely used in the United States. The decision was reached later that it should be in the Pharmacopeia because of the use of the U. S. P. in many other countries. The drug itself is of great value as a trypanosomicide, particularly in the control of African sleeping sickness. A single intravenous dose of 1 Gm. is claimed to protect an individual from this disease for as long as 3 months.

Suramin Sodium is sold by Winthrop-Stearns as *Naphuride Sodium*. It is packaged in 1 Gm. ampuls as a dry sterile powder.

Testosterone
Testosterone Pellets

Both methyltestosterone and testosterone propionate were recognized in the U. S. P. XIII. The former is given orally, and the latter is most frequently given in oil solution by intramuscular injection.

Testosterone was admitted to the U. S. P. XIV by reason of its use in pellet form for tissue implantation. This procedure is carried out by making a small incision and inserting a pellet in the tissue or by using a special instrument known as a pellet injector. The number of pellets implanted at one time is governed by the established need of the patient which is first determined by the response to testosterone propionate by intramuscular injection. If 50 mg. of testosterone propionate weekly is adequate, the implantation of 4 pellets of 75 mg. each should be sufficient. If 75 mg. of testerone propionate is needed, the implantation of 6 pellets is indicated. These pellets provide continuous medication of the patient for 6 to 10 months. This type of therapy supplies a much more continuous and even blood level of the androgen than does the oral or intramuscular route. It is particularly useful where treatment is necessarily prolonged as in male hypogonadism, eunuchoidism, etc. With proper technic the implantation is not painful nor does it leave any marked scar tissue. Testosterone Pellets are sold as 75 mg. pellets by the Schering Corp. under the proprietary name *Oreton-F*.

Theobromine Calcium Salicylate
Theobromine Calcium Salicylate Tablets

This is a double salt or complex in molecular proportions of theobromine calcium and calcium salicylate. It is a white, odorless

powder with a saline taste. Theobromine Calcium Salicylate is used as a diuretic and as a coronary vasodilator. The usual dosage is 0.5-1.0 Gm. 3 times a day. It is sold by the American Pharmaceutical Co. under its official name and by the Bilhuber-Knoll Corp. as *Theocalcin Powder* and *Theocalcin Tablets.*

Thrombin

This is a sterile protein substance prepared from prothrombin of mammalian origin through interaction with added thromboplastin in the presence of calcium. The product is a white or grayish white, amorphous substance prepared by the use of one of the several processes of drying from the frozen state. It is prepared for use by addition of a prescribed amount of sterile normal saline solution which restores it to a solution which can be applied topically to arrest capillary bleeding. Thrombin acts by a reaction with blood fibrinogen to form fibrin, the structural substance of a blood clot. The label of the product must indicate its strength in terms of units, and the package must be stored at a temperature between 2 and 10°.

Thrombin as *Thrombin, Topical* is available from Cutter Laboratories in vials, containing 2500 and 5000 units. It is also available from Parke, Davis & Co. in vials containing 1000 and 5000 units and from The Upjohn Co.

Trimethadione
Trimethadione Capsules
Trimethadione Tablets

This substance has the chemical name 3,5,5-trimethyl-2,4-oxazolidinedione. It is a white, crystalline, granular substance with a slight camphor-like odor. It should be stored preferably at a temperature not exceeding 30°.

Trimethadione is an anti-epileptic drug which acts as an anticonvulsant. It is of value principally in seizures of the petit mal type and in psychomotor seizures. In the latter type, as in cases complicated by grand mal seizures, the use of phenobarbital or diphenylhydantoin sodium with trimethadione is usually necessary. If the combination results in an increase in grand mal seizures, the relative dose of the two drugs should be altered.

Trimethadione does not often cause toxic reactions, but photophobia, gastric irritation and skin eruptions may require its temporary withdrawal or a reduction in its dose. In rare cases it may cause

aplastic anemia, and to guard against this possibility patients receiving the drug for extended periods should have regular blood examinations. It is also contraindicated in patients with known blood dyscrasias or advanced renal or hepatic disease.

The adult dose usually is 1 to 2 Gm. daily in divided doses, but the optimum dosage level must be established for each individual patient. Trimethadione Capsules are sold by Abbott Laboratories as *Tridione Capsules*. A special flavored tablet intended for children is sold by the same company as *Tridione Dulcet Tablets*.

Tripelennamine Hydrochloride
Tripelennamine Hydrochloride Tablets

This is the chemical substance N-benzyl-N^1,N^1-dimethyl-N-2-pyridylethylenediamine hydrochloride. It is a white crystalline powder which slowly darkens on exposure to light. Tripelennamine Hydrochloride is the well-known antihistamine sold by Ciba Pharmaceutical Products, Inc. as *Pyribenzamine*.

The therapeutic applications of the antihistamines are so extensive and common that it is not considered necessary to present them in this review.

Tubocurarine Chloride
Tubocurarine Chloride Injection

This is essentially pure d-tubocurarine chloride obtained from *Chondodendron tomentosum* and related species. Tubocurarine is a quaternary base alkaloid which in small doses blocks the myoneural transmission of nerve impulses to skeletal muscle. Larger doses depress ganglionic transmission in the autonomic nervous system. It is used clinically in a number of conditions to reduce the tone of contractile skeletal muscle. Tubocurarine chloride is often used with anesthetics, particularly those which themselves do not produce good muscle relaxation. Thus it is often used as an adjunct in cyclopropane or thiopental sodium anesthesia. When used with ether anesthesia only about one-third the dosage of tubocurarine chloride is required as compared with the dose used with other anesthetics. Tubocurarine chloride is also used in spastic and athetoid states, particularly for spastic children who are engaged in a program of muscle training. It is used, furthermore, to soften the convulsions in shock therapy, in the reduction of fractures in orthopedic procedures and in the diagnosis of myasthenia gravis.

Overdosage of tubocurarine chloride causes respiratory failure due to a paralysis of the diaphragm and intercostal muscles. The antidote is neostigmine methylsulfate injection 1-2000.

The biological unit equals the activity of 0.15 mg. of pure d-tubocurarine chloride pentahydrate. A reference standard is provided by the Pharmacopeia for the official assay.

The dosage of tubocurarine chloride given depends upon the patient and the degree of muscle relaxation required. Patients with myasthenia gravis, in whom it is used as a diagnostic test, are extremely sensitive to the drug.

Tubocurarine chloride is available in injection form in two strengths. One contains 3 mg./cc., and it is available from both Abbott Laboratories and E. R. Squibb & Sons. The latter company also supplies a high potency product containing 15 mg./cc. This is specifically intended for use with thiopental sodium for intravenous anesthesia.

Tyrothricin
Tyrothricin Solution
Tyrothricin Spray
Tyrothricin Troches

Tyrothricin is an antibacterial substance produced by the growth of *Bacillus brevis*. It consists principally of gramicidin and tyrocidine, the tyrocidine usually being present as the hydrochloride. Tyrothricin is required to possess a potency not less than 90 per cent that of the U. S. P. Reference Standard. It is a white, grayish white, or brownish powder which is almost odorless and tasteless. Tyrothyricin is practically insoluble in water but soluble 1 part in 15 parts of alcohol.

This antibiotic is effective particularly against gram positive organisms and has an antibacterial spectrum somewhat similar to that of penicillin. It differs from penicillin in that it may be used only topically since it is toxic when injected causing hemolysis and it is not effective orally.

The official solution is a solution in alcohol with the addition of a wetting agent permitted. The alcoholic solution is diluted with water before it is used which results in a colloid dispersion of the tyrothricin. This dispersion which contains 0.5 mg./cc. is intended for topical use or for the irrigation of body cavities. When used in the eye the finished dispersion contains only 0.3 mg./cc. An alcoholic

solution corresponding to the official Solution and containing 2½ per cent of tyrothricin is sold by Sharp & Dohme, Inc.

Tyrothricin Spray of the Pharmacopeia is a solution of tyrothricin in water made with the aid of suitable, harmless solubilizing and wetting agents. It may contain both a small amount of alcohol and a suitable vasoconstrictor. This product is intended for use in the nose applied with a tampon, a dropper or an atomizer. The proprietary product *Prothricin* sold by Sharp & Dohme, Inc. conforms to the official monograph for Tyrothricin Spray as do *Gluco-Thricil* sold by Parke, Davis & Co. and *Wyamine-Tyrothricin* sold by Wyeth, Inc. Each of these contains 0.02 per cent tyrothricin with an added vasoconstricting agent.

The monograph for Tyrothricin Troches in the Pharmacopeia is so broadly written that any troche containing this antibiotic conforms to the official requirements, provided its content of tyrothricin lies between 90 and 120 per cent of the labeled potency. Tyrothricin troches containing some suitable local anesthetic, such as ethyl aminobenzoate, have become very popular in the treatment of throat infections caused by tyrothricin susceptible organisms. It is important that these troches be allowed to dissolve slowly in the mouth and that they are not chewed. The prolonged effect by slow solution of the troche in the saliva is desirable. Tyrothricin troches which are available include:

Tyrozets—Sharp & Dohme, Inc.
Lozilles—White Laboratories, Inc.
Teeds—The Warren-Teed Products Co.
Pemzoles—Pitman-Moore Co.

The use of tyrothricin in the impregnation of the compress of Adhesive Absorbent Bandage is permissible according to the official text of this latter's monograph. Such a product is sold by Johnson & Johnson as *Tyrothricin Band-Aid*.

Vanilla
Vanilla Tincture

Both of these products were official in the N. F. VIII. They were adopted by the U. S. P. XIV as pharmaceutic necessities since the tincture is an ingredient of Cacao Syrup.

Vasopressin Injection

This product is a sterile solution in water for injection of the water soluble pressor principle of the posterior lobe of the pituitary body of healthy domesticated animals used for food by man. Each cc. possesses a pressor activity equivalent to 20 U. S. P. Posterior Pituitary Units.

Vasopressin Injection is a solution which has twice the pressor potency of Posterior Pituitary Injection U. S. P. but less than 1 unit of oxytocic activity per cc. It is employed in instances where the effect of the pressor principle is desired with a minimum of oxytocic action. Thus it is used to raise blood pressure, to relieve intestinal atony and that of the bladder following surgery and for its antidiuretic action in diabetes insipidus.

Vasopressin Injection is supplied by Parke, Davis & Co. under the name *Solution Pitressin* in 0.5 and 1.0 cc. ampuls. The dose is 0.3 to 1.0 cc. given intramuscularly and repeated as required.

Vitamin B_{12}
Vitamin B_{12} Injection

Vitamin B_{12} is a cobalt-containing substance produced by the growth of suitable microbial organisms or obtained from liver. It is a dark red crystalline substance 1 part of which is soluble in 80 parts of water.

It is now believed that vitamin B_{12} is the true antipernicious anemia factor. It is said to be the most active biochemical substance known since only about 1 microgram per day is required to maintain normal erythropoiesis. In all likelihood, vitamin B_{12} is the substance formerly thought of as the "extrinsic factor". In pernicious anemia the individual lacks that gastric factor called the "intrinsic factor" and thus the dietary B_{12} is not utilized. It is known that the neutralized gastric juice of normal persons given orally with vitamin B_{12} to patients with pernicious anemia activates it so that it is effective. This "intrinsic factor" of normal gastric juice was just recently reported to have been isolated.

When vitamin B_{12} is given by injection, the intrinsic factor is not needed for its utilization, and the parenteral route is at present the favored method to administer this substance, at least in pernicious anemia. The injection is given both intramuscularly and subcutaneously.

Vitamin B_{12} has an advantage over liver extract in that it is a pure substance and causes no reaction in patients who are sensitive to liver.

In addition to its use in pernicious anemia, vitamin B_{12} is of value in nutritional macrocytic anemia, tropical and non-tropical sprue and megaloblastic anemia of infants.

Although the daily requirement is about 1 microgram, it is usually given in doses of 10 to 15 micrograms, or even more, at appropriate intervals. Vitamin B_{12} is stored by the liver, and consequently a "depot" effect can be produced with doses in excess of the immediate requirement.

It is quite likely that vitamin B_{12} will be used to an increasing extent in medicine. Its combination with folic acid, liver and iron will lead to many new proprietary products. It is already known that folic acid seems to potentiate its effect. Other uses of vitamin B_{12} than in anemia are suggested by controlled experiments which indicate that its oral use causes a marked rise in the growth curve of physically retarded children.

Vitamin B_{12} Injection is available under a variety of proprietary names. Among these are:

Be-Dodec—Schieffelin & Co.
Betalin 12—Eli Lilly & Co.
Bevidox Crystalline—Abbott Laboratories.
Cobione—Merck & Co.
Cytobex—Parke, Davis & Co.
Dodecavite Crystalline—U. S. Vitamin Corp.
Dodex Injectable—Organon, Inc.
Rubramin—E. R. Squibb & Sons.

Zinc Gelatin

This is often referred to as Zinc Gelatin Boot. It is a firm plastic mass containing gelatin, zinc oxide, glycerin and water. Zinc Gelatin may be prepared by several formulas, but the official product is based on the formula used at the University of Iowa Hospital. It is used most often to apply the type of pressure bandage known as a "gelatin boot" for the treatment of various conditions but principally varicose ulcers. In this direction it has given excellent results. The technic for applying it is as follows:

The patient should be reclining with leg elevated for at least ½ to 1 hour. Any exudate surrounding, or in an open lesion, should be gently cleansed with a mild detergent.

The paste is liquefied on a water bath to the consistency of heavy cream and allowed to cool just enough so that it is tolerable to the patient. The application is best performed with an assistant. The patient helps hold the leg elevated with a towel behind the knee. A 2" bandage is best used to apply a smooth boot. The leg is rapidly coated from instep to knee and the paste applied with an ordinary paint brush. Beginning on the foot the bandage is applied in circular fashion up to the knee overlapping about 1/3 of the preceding layer. The assistant constantly wets the bandage as it is applied with a liberal amount of the paste. Two to three rolls of bandage are used depending on the desired boot thickness, and 480 grams of paste should be sufficient. The gelatin is allowed to set for about 5 minutes, then the boot is sprinkled liberally with talcum. Finally, a single layer of bandage is rolled over the boot and secured with ½ inch adhesive. One inch adhesive is fashioned around the heel to enclose it. The whole boot is then dried with an electric blower. The bandage should be applied smoothly, molded like plaster of Paris, and may be applied snugly. If there is an open ulcer, a paste saturated 4 x 4 gauze square should be applied directly to the lesion before the boot is fashioned. The boot will remain intact for 2 to 6 weeks, depending on the amount of discharge from the lesion and on how rapidly it becomes loose.

Zinc Oxide Paste

This product, also known as Lassar's Plain Zinc Paste, was official in the N. F. VIII. Its use is considered of sufficient value in dermatology to warrant its inclusion in the U. S. P. XIV.

STUDIES ON THE FORMATION OF INVERTASE BY NEUROSPORA CRASSA*

By Louis Gershenfeld ** and Aaron E. Wasserman ***

THE influence of the physical environment and the chemical composition of the medium on the formation and the activity of the enzyme invertase have been investigated by many workers. However in their studies, use was made of several species of yeast and molds with varying metabolic characteristics, with the result that many of the conclusions are contradictory. Fernbach (1) indicated that the production of invertase by yeast was not greatly influenced by the carbohydrate source present in the medium but that the nitrogenous substances played an important role in enzyme formation. On the other hand, Euler and his co-workers (2) reported that preliminary treatment of yeast with sucrose resulted in a 300% increase in invertase activity. Enhancement of enzyme formation occurred not only with the specific substrate (sucrose) and the products produced by its hydrolysis (glucose and fructose), but such unrelated sugars as maltose (1) and mannose (3) also served as stimulatory agents. Using species of *Aspergillus* and *Penicillium*, Kertesz (4, 5) found that invertase formation occurred when raffinose or sucrose was present in the medium. Prigsheim *et al.* (6) found that, depending on the carbohydrate source in the medium, *Aspergillus wentii* contained either a fructo-invertase, which acted on the fructoside linkage of the sucrose molecule, or a glucosidase, which hydrolysed sucrose at the glucose moiety.

Recognizing the importance of the nitrogenous components of the medium on invertase formation in yeast, Euler (7) showed that

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the natural substance "yeast water" enhanced enzyme production; whereas asparagin and ammonium sulfate had little effect. On the other hand, using *P. glaucum* in his experiments, Kertesz (8) demonstrated that asparagin in the medium caused a doubling of invertase formation, while the presence of peptone completely inhibited enzyme production.

The effect of temperature, pH, aeration of medium, and age of the organisms on the invertase activity has been discussed by Meisenheimer (9), Euler (7), and Kertesz (8).

Went (10, 11) reported on the enzymes present in the mold, *Monilia sitophila* (at present classified as *Neurospora sitophila*), including studies on the production of invertase. The greatest invertase activity was found when the organism was grown on 5% glucose, and little or no enzyme formation with lactose, raffinose, glycerin, and peptone as substrates. However, Went measured the invertase activity of the medium. It has been shown that invertase is an endoenzyme with less than 10% of the total activity appearing in the medium (12). Thus Went was determining an uncertain quantity varying with the degree of degradation of dead cells and the permeability of those living.

Our presentation is a report on some of the factors influencing the formation of invertase in *Neurospora crassa*.

Experimental

Organism. The organism used in these experiments was the wild strain of *Neurospora crassa* obtained through the courtesy of Dr. B. S. Gould, Department of Biology, Massachusetts Institute of Technology. It is to be noted that, due to the inherent variability of the organism (13, 14), direct comparison of results is justified only when all units are inoculated at the same time, from the same spore suspension, and treated in an identical manner throughout the course of the experiment. Even when such precautions are taken, deviations may occur.

Growth Medium. In order to facilitate the addition of substances to be studied, the growth medium is prepared in several stages.

a. Basal medium. The basic salt solution consists of:

Monobasic Potassium Phosphate (KH_2PO_4)*	1.0 Gm.
Magnesium Sulfate ($MgSO_4 7H_2O$) U.S.P.	1.5 Gm.
Sodium Chloride (NaCl)	0.1 Gm.
Calcium Chloride ($CaCl_2$, anhyd.)	0.1 Gm.
Boron (as H_3BO_3)	0.01 mg.
Molybdenum (as MoO_3)	0.02 mg.
Iron (as $FeSO_4 7H_2O$)	0.20 mg.
Manganese (as $MnSO_4 4H_2O$)	0.02 mg.
Copper (as $CuSO_4 5H_2O$)	0.10 mg.
Zinc (as $ZnSO_4 7H_2O$) U.S.P.	2.0 mg.
Phosphate buffer (KH_2PO_4—Na_2HPO_4) 0.5 M.+	100 ml.
Water, distilled	1000 ml.

*All chemicals used are Merck reagent grade unless otherwise specified.

+ The buffer solution is adjusted to pH 5.5 or pH 6.5 as needed. Other pH values are obtained by the addition of N/2 HCl or N/1 NaOH to the basal medium.

This solution is prepared in 10 liter quantities and 1 liter volumes are removed as required. Biotin is added just before use to give a concentration of 5×10^{-6} Gm. per liter.

b. Complete Medium. This consists of the basal medium to which has been added 0.5% ammonium tartrate and 0.1% ammonium nitrate. The substitution of other compounds as the nitrogen source is indicated in the particular experiment.

c. Sufficient carbohydrate, or carbon source, is added to the *complete medium* to give a 2% concentration of the substance added. The carbohydrate used is indicated in the particular experiment.

Sporulation Medium—To prepare a solid medium for the production of conidia for inoculation purposes the following substances are added to the *complete medium* (pH 5.5): 2% glucose, 0.5% malt extract (Difco), 50 mg.% casein hydrolysate (G. B. I.), 2% agar (Difco), 0.5% yeast extract (Difco).

N. crassa is streaked on slants of the sporulation medium and incubated at 26° C. for 5 to 6 days. At the end of this time enough

conidia are present for the preparation of a suspension to be used in the inoculation of the culture flasks. The conidial suspension is made by adding 10 ml. sterile distilled water to the slants and gently agitating.

Test Procedure. Cultures are made in 125 ml. Erlenmeyer flasks. The flasks, containing 25 ml. of the *complete medium* with the specific carbon source, are autoclaved at 115.5°C. (10 pounds pressure) for 20 minutes. The flasks are then inoculated with 0.4 ml. of spore suspension and incubated at 26°C. During the period of incubation the flasks are shaken gently twice daily to submerge the mycelial mat and prevent the formation of aerial conidia. At the end of the incubation period the mycelial mats are removed and washed several times with distilled water to remove any adhering medium. The mycelia are placed in 25 ml. of 4% sucrose solution prepared with 0.05 M phosphate buffer at pH 4.65. The optical rotation of the sucrose solution is determined immediately with a saccharimeter, and change in rotation is followed hourly. At the end of the experiment the mycelia are removed from the sucrose solutions, pressed dry with filter paper, allowed to dry spontaneously at room temperature overnight, and weighed.

a. *Calculations:* At low concentrations of sucrose, the hydrolysis of this sugar is considered to be a monomolecular reaction and the rate of reaction determined from the formula:

$$k = \frac{2.303}{t} \log \frac{a}{a-x}$$

where k = rate of reaction, t = time in minutes, a = initial concentration of sucrose, $a-x$ = concentration of sucrose at time t. However, the rate of reaction has been found to vary, and despite such precautions as alkalinizing the sucrose solution with sodium bicarbonate (15) before reading in the saccharimeter, the values of k increased with time. It was decided, therefore, that in those studies the course of the reaction might be more easily followed by the value a , and that $a/a-x$ would be used to determine

$$\frac{a-x}{\textit{mycelial weight}}$$

the invertase activity per mg. dry weight of mycelium.

Results

Influence of Carbon Source on Invertase Formation

In some preliminary experiments it was found that the greatest invertase activity occurred when the organism was grown on the *basal medium* containing levulose, raffinose, or xylose as the carbon source. Growth on media containing sucrose or glucose gave rise to mycelia with low invertase activity (Fig. 1.). This led to further investigation of the growth requirements for invertase formation in *N. crassa*.

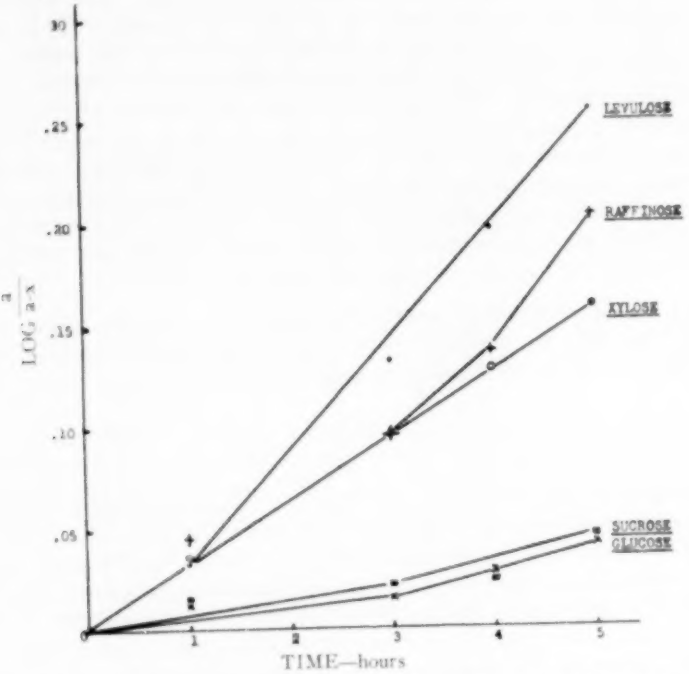

FIG. 1. THE INVERTASE ACTIVITY OF *N. Crassa* GROWN ON VARIOUS SUGAR MEDIA (pH 5.5) FOR SEVEN DAYS.

(1) *The effect of the pH of the growth medium and age of mycelium on the formation of invertase.* A series of flasks were prepared containing the *basal medium* and 2% concentrations of glucose, levulose or sucrose, adjusted to various pH levels. On the

3rd, 5th and 7th day of growth the mycelia were removed from one flask of each sugar at the various pH levels, and the invertase content determined. When the mycelium was grown on levulose, the optimum pH for invertase formation lay between pH 6.0 and 6.5; when glucose was the carbon source, the optimum pH range was pH 7.0 to 7.5. At these optimum pH levels maximum enzyme formation occured on the 5th day of growth, dropping off by the 7th day. By contrast, invertase was formed more slowly at the other pH levels, but there was a continuous increase in the enzyme concentration up to the 7th day. (See Table I.)

TABLE I

The Effect of the Age of *Neurospora crassa* and the pH of the Growth Medium on the Formation of Invertase in the Mycelium Growing on the Specific Substrate (Sucrose) and its Hydrolysis Products.*

		Days of Growth					
		3rd		5th		7th	
2% sugar in medium	pH of medium	Mycelial wt. mg.	$Kx10^5$	Mycelial wt. mg.	$Kx10^5$	Mycelial wt. mg.	$Kx10^5$
Glucose	4.0	25.1	28.0	42.0	39.0	90.0	219
	5.0	29.6	35.9	52.1	49.6	99.4	305
	5.5	41.0	51.4	77.3	282.0	100.0	354
	6.0	43.2	83.7	82.1	278.0	104.9	371
	6.5	46.3	107.0	89.4	332.0	130.8	427
	7.0	47.8	158.0	91.0	473.0	117.0	488
	7.5	55.2	171.0	89.0	835.0	101.8	412
Sucrose	4.0	53.7	49.3	106.0	265.0	104	432
	5.0	66.2	85.0	109.8	337.0	—	—
	5.5	57.7	138.0	110.0	1110.0	108	809
	6.0	81.3	200.0	130.0	1120.0	113	769
	6.5	80.4	313.0	133.0	1146.0	121	1052
	7.0	38.8	420.0	108.6	1183.0	114	843
	7.5	60.3	604.0	108.0	944.0	110	939
Levulose	4.0	15.0	120.0	24.7	114.0	113.8	461
	5.0	25.5	91.0	57.4	250.0	91.9	274
	5.5	52.4	90.0	43.4	260.0	114.7	699
	6.0	22.9	161.0	106.9	1080.0	115.0	506
	6.5	58.2	243.0	118.0	880.0	94.9	406
	7.0	29.4	152.0	66.8	427.0	90.3	471
	7.5	—	—	73.8	446.0	76.8	588

K = rate of reaction

* Each sugar series was set up independent of the others; therefore comparison of results between sugars is not valid.

Mycelia growing on sucrose medium also form their maximum invertase on the 5th day, but the optimum pH range appears to vary from pH 6.5 to 7.5 on the different days tested. This may be due to the fact that assimilation of sucrose by *N. crassa* is a complex process. It has been shown by one of us (16) that when sucrose is hydrolysed the glucose moiety is preferentially utilized, being almost entirely exhausted before the levulose is used. Possibly in the early stages of growth, the invertase formation on sucrose assumes the identical characteristics of formation as on glucose (See Table I). By the 5th day levulose is being incorporated into the mycelial protoplasm, and the optimum pH for enzyme formation drops to pH 7.0. On the 7th day the organism, utilizing levulose exclusively, has the optimum pH for enzyme formation characteristic of growth on levulose.

It is interesting to note that, although the media were highly buffered at the beginning of the experiment, the pH of the media decreased as growth of the organisms continued. A low point was reached on the 3rd or 4th day, which had no relationship with the level of the original pH. By the 5th day the pH of the media began to increase, finally approaching the original pH level, or becoming more alkaline, as in some instances. The lowest pH attained (approximately pH 3.5) occurred in all sugar media originally buffered to pH 5.0.

In view of the above observations, attempts were made to control the pH values at the original levels. However, due to experimental difficulties, it was not possible to maintain the original pH in the different flasks in each series (See Table II).

TABLE II

Change in pH

Original pH	Days of Growth				
	2	*3*	*4*	*5*	*7*
4.0	3.74	3.55	3.59	3.83	4.3
5.0	3.70	3.51	3.52	3.69	4.27
5.5	3.82	3.72	3.91	4.54	4.64
6.0	5.42	4.79	5.3	5.75	5.86
6.5	6.24	5.94	5.8	6.19	6.47
7.0	6.71	6.49	6.41	6.62	6.83
7.5	7.0	6.75	6.70	7.0	7.2

The effects of the pH of the growth medium and the age of the organisms on the invertase information by *Neurospora* were

determined on a number of carbohydrates. These were made up in 2% solutions in the *basal medium* and adjusted to pH 5.5 and 6.5 (the pH 5.5 level was chosen as it is the reaction of the medium given in the literature of *Neurospora* experimentation). On the 5th and 7th days, mycelia were removed and their invertase content determined. On all the sugars in which growth occurred, the mycelia grown at pH 6.5 showed the highest invertase activity by the 5th day, remaining stationary or dropping off slightly on the 7th day of growth. (See Table III.) Growth at pH 5.5 yielded mycelia low in enzyme activity on the 5th day, with a slight increase by the 7th day. The sugars giving rise to mycelia with the highest enzyme content were levulose, maltose, invert sugar (a mixture of equal parts of glucose and levulose), and raffinose. Growth on raffinose was complicated by very active sporulation despite all efforts to keep the mycelium submerged. A small quantity of mycelium was obtained, but this had a high invertase activity per mg. dry weight.

TABLE III

The Effect of the Age of *Neurospora crassa* and the pH of the Growth Medium on the Formation of Invertase in Mycelia Growing on Various Sugars.

2% Sugar in medium	pH of medium	Days of Growth 5th		7th	
		Mycelial wt. mg.	a/a-x mycel. wt.	Mycelial wt. mg.	a/a-x mycel. wt.
Xylose	6.5	108.5	0.0481	111.8	0.042
	5.5	132.5	0.022	90.6	0.035
1% Glucose + 1% Levulose	6.5	110.9	0.162	104.5	0.024
	5.5	92.7	0.032	98.1	0.042
Glucose	6.5	91.5	0.107	100.6	0.071
	5.5	73.2	0.035	78.4	0.034
Levulose	6.5	96.7	0.558	87.2	0.309
	5.5	86.2	0.031	86.9	0.077
Raffinose	6.5	22.2	0.121	23.4	0.072
	5.5	36.4	0.051	31.8	0.105
Maltose	6.5	104.0	—	115.4	—
	5.5	89.4	0.060	85.1	0.058

Arabinose, inulin, galactose, dulcitol, formate, citrate, succinate, malate, and ammonium tartrate were also employed as carbon sources, but growth on the media containing these compounds was so sparse that enzyme activity could not be determined.

(2) *The effect of carbohydrate concentration.* It had been found that the carbohydrates supplied in 2% concentration were completely utilized by the 4th or 5th day of growth. In order to note whether the invertase content of the organisms might be increased if sufficient carbon source were present throughout the growth period, glucose, levulose, or sucrose were added to the *basal medium* in concentrations of 1, 2, 4, 6, 8, and 10%. The results, tabulated in Table IV, show that the greatest invertase activity occurred in the mycelia grown in 1 to 2% concentrations of the sugars, decreasing as the sugar concentration increased.

(3) *The effect of pH and carbon source in the sporulation medium.* The previous experiments indicated that the optimum cultural conditions for invertase formation occurred when 2% levulose was supplied to the *basal medium* having a pH of 6.5. The question arose as to whether growing the spores on the glucose agar slants at pH 5.5, as was done, influenced the formation of invertase in the mycelium arising from the spores. Although gross changes in the invertase production would probably indicate a change in the genetic structure of the organisms, it was felt minor variations might occur because of the differences in the nutrition of the spores. A sporulation medium was prepared, therefore, containing glucose, levulose, or sucrose at pH 5.5, and glucose at pH 6.5. Six days after seeding, spore suspensions were made, and each was inoculated into a growth medium containing 2% concentrations of glucose, levulose, or sucrose at pH 6.5. After 5 days of growth at 26°C., the invertase activities of the mycelia were determined (Table V). Spores grown on glucose agar at pH 6.5 gave rise to the heaviest mycelial growth, but contained the least amount of invertase per mg. mycelial weight. Spores grown on levulose agar formed the smallest mycelial mat but gave rise to the greatest invertase activity per mg. mycelial weight on all 3 growth media. The invertase activity of mycelia from all four spore suspensions was lower on the glucose growth medium than on sucrose or levulose containing media.

TABLE IV

The Effect of the Concentration of Carbohydrate in the Growth Medium on the Invertase Formation in *N. crassa*.

Sugar Conc. %	Levulose 1	2	4	6	8
mycel. wt. mg.	47.6	97.7	133.3	126.9	105.2
a/a-x / mycel. wt.	0.079	0.080	0.050	0.028	0.029

Sugar Conc. %	Glucose 2	6	8	2*	4*	10*
mycel. wt. mg.	101.2	189.7	161.3	92.5	133.5	182.8
a/a-x / mycel. wt.	0.057	0.012	0.013	0.016	0.013	0.007

Sugar Conc. %	Sucrose 2	6	8	2*	4*	10*
mycel. wt. mg.	85.6	154.6	161	88	148	120.5
a/a-x / mycel. wt.	0.061	0.024	0.015	0.019	0.013	0.012

*These values are the results of another set of experiments.

TABLE V

The Effect of pH and Carbohydrate Source of the Sporulation Medium on the Formation of Invertase by *N. crassa* Growing in Media Containing 2% Glucose, Levulose, or Sucrose.

Sporulation Medium	pH 5.5			pH 6.5
	Lev.	Gluc.	Suc.	Gluc.
Growth Medium	Levulose			
Mycel. wt. mg.	16.5	32.6	30.0	33.2
a/a-x / mycel. wt.	0.101	0.076	0.077	0.062
Sporulation Medium	pH 5.5			pH 6.5
	Lev.	Gluc.	Suc.	Gluc.
Growth Medium	Glucose			
Mycel wt. mg.	27.1	38.1	38.4	53.2
a/a-x / mycel. wt.	0.048	0.036	0.034	0.029
Sporulation Medium	pH 5.5			pH 6.5
	Lev.		Suc.	Gluc.
Growth Medium	Sucrose			
Mycel. wt. mg.	37.1		47.2	54.7
a/a-x / mycel. wt.	0.077		0.074	0.067

Influence of Nitrogen Source on Invertase Formation

Although it is possible for organisms to convert sugars, by transamination, into certain amino acids essential for protein synthesis (17), it is necessary to supply some form of nitrogen to the organism. Molds vary in their nitrogen requirements, some being able to assimilate proteins and amino acids, others requiring only inorganic nitrogen. Boaz (18) indicated that the amino acids must be deaminated before assimilation and that this is a process which requires considerable energy, therefore many molds preferentially utilize NH_4^+ and NO_3^- salts. However, the ability of the nitrogenous material to serve as a source for the protoplasmic matter of the organism is no indication of the ability of the organism to convert the nitrogen into enzyme protein. The hydrolysis of the nitrogenous substances may give rise to products which inhibit the formation of an enzyme.

(1) *The effect of several nitrogen sources on invertase formation.* A series of nitrogenous compounds were incorporated into the *basal medium*, (pH 6.5) with levulose as the carbon source. After 5 days growth at 26°C. the invertase activity of the mycelia was determined (Table VI). It was found that *Neurospora crassa* had best utilized the NO_3^- or NH_4^+ salts and urea in the synthesis of cellular material, giving rise to mycelia of approximately equal weight. However, growth on urea provided the organism with the greatest yield of invertase activity. Sodium nitrate, ammonium nitrate, ammonium tartrate, and combinations of the last 2 compounds were also utilized for good enzyme production, but the complex nitrogen sources—peptone, casein hydrolysate, and yeast extract were poorly assimilated for either cellular growth or enzyme formation.

The optimum concentrations of ammonium nitrate and ammonium tartrate for maximum invertase formation were determined, and it was found that 50 mg. per 25 ml. medium of each compound provided the most favorable conditions. However, taking into consideration the actual concentration of nitrogen present in the medium at optimal enzyme formation, it was found that ammonium nitrate supplies 10 times as much nitrogen as the ammonium tartrate. It appeared that quantities of ammonium nitrate in excess of 2 mg. per ml. medium were inhibitory to enzyme formation. The invertase activity of mycelia grown on media containing 4 mg. per ml. of ammonium nitrate was very small although the heaviest mycelium was

produced. This may be due to toxic breakdown products, possible traces of HNO_2, which are formed in a concentration high enough to inhibit enzyme formation without affecting the growth of the organism.

TABLE VI

The Effect of Various Nitrogen Sources on the Formation of Invertase in *N. crassa*.

Nitrogen Compound	Gm. atoms N/25 ml. medium	Mycelial wt.-mg.	a/a-x / mycel. wt.
(a) NH_4 Tartrate	0.00042	70.0	0.0545
(b) NH_4 Tartrate	0.00091	89.5	0.1109
NH_4 H_2PO_4	0.0011	66.8	0.0428
(c) NH_4NO_3	0.0048	86.6	0.0944
$(NH_4)_2SO_4$	0.00079	79.5	0.0592
$(NH_4)_2SO_4$	0.00127	78.8	0.0226
KNO_3	0.0014	73.2	0.0634
$NaNO_3$	0.0029	82.2	0.0898
NH_4 Tartrate (a) + $(NH_4)_2SO_4$ (c)	0.0046	100.5	0.1082
NH_4 Tartrate (b) + $(NH_4)_2SO_4$ (c)	0.0051	84.4	0.2061
Urea	0.0075	83.9	0.2888
Casein Hydrolysate	1 mg. in 25 ml. medium	52.2	0.040
Peptone (Difco)		34.2	0.0381
Yeast Extract		49.3	0.0571

When urea was supplied as the nitrogen source in a medium containing levulose at pH 6.5, it was found that the maximum invertase activity occurred in the mycelium grown on 125 mg. urea per 25 ml. medium (Table VII). Although the concentration of nitrogen in urea is high, the mycelial weight of *N. crassa* grown on urea-containing media was not out of proportion to the weights of mycelia grown on other nitrogen sources. In fact, increasing the urea concentration beyond 50 mg. per 25 ml. medium caused a sharp decrease in the mycelial weight.

TABLE VII

The Effect of Various Concentrations of Urea on the Invertase Formation in *N. crassa*.

	Urea Concentration				
	Control*	50 mg.	125 mg.	250 mg.	500 mg.
Gm. atoms N in 25 ml. medium	0.0064	0.0154	0.039	0.078	0.156
Mycelial wt. mg.	67.0	81.8	41.6	22.0	15.0
$\frac{a/a\text{-}x}{\text{mycelial wt.}}$	0.0673	0.1161	0.3240	0.0810	0.0958

In view of the results obtained, it appears that maximum growth does not coincide with maximum invertase production, and that neither factor can be correlated with the concentration of nitrogen in the medium. Neurospora can form its maximum invertase when grown on 0.00083 Gm. atoms of nitrogen contained in ammonium tartrate, or on 0.039 Gm. atoms of nitrogen from urea. The growth, however, is limited by factors other than nitrogen concentration mentioned above.

Optimum pH for Invertase Activity

Sorenson (19) showed that the invertase activity was a function of the H^+ concentration and was independent of the amount of acid or the anion used. He demonstrated that the H^+ ion concen-

* Contained 25 mg. ammonium nitrate and 125 mg. ammonium tartrate in 25 ml. medium.

tration for maximum activity of yeast invertase was $10^{-4.6}$ or pH 4.6. This was later confirmed by Fales and Nelson (*20*). Michaelis and Davidsohn (*21*) reported a broad optimal zone for yeast invertase activity lying between pH 3.5 and 5.5. Although the optimum pH for yeast invertase activity had been accepted as being pH 4.6, Adams, Richtmayer, and Hudson (*22*) have recently reported a highly purified yeast invertase preparation with a maximum activity at pH 5.0 to 5.5. It has also been shown that invertase from various sources had different optimum pH values. Euler (*23*), working with Penicillium sp., reported an optimal range for the mold invertase lying between pH 4.0 and 6.0.

In view of the differences in the values reported, it was decided to determine the pH at which the maximum invertase activity of *Neurospora crassa* occurred. A series of flasks was prepared, each containing 25 ml. *complete medium* (pH 6.5) with 2% levulose. After inoculation and incubation at 26°C. for 5 days, the mycelia were removed, washed and placed in 4% sucrose solutions adjusted to the various pH levels indicated in Fig. 2. The optimum pH range for maximum invertase activity was found to lie between pH 5.0 and 5.5. Repeated experiments, performed with different sets of mycelia consistently fell within this range, with an occasional series showing a maximum activity at pH 4.8. Several experiments were performed with mycelia grown at pH 5.5 and pH 7.0. These, too, fell within the optimal range, pH 5.0 to 5.5, indicating that the pH of the growth medium does not affect the pH at which the enzyme displays its maximum activity.

Cell-free Preparations

The use of cell-free preparations or extracts for the measurement of enzyme activity was investigated. The methods of preparation included: grinding the mycelium with sand, repeated freezing and thawing, an attempt at autolysis in the presence of toluene, and employing a preparation of dry mycelium after treatment with acetone or dioxane. Inasmuch as invertase activity was not evident when these preparations were used, treatment to obtain cell-free preparations did not appear worthwhile and accordingly was discontinued.

Discussion

Kuhn (*24, 25*) has demonstrated that the enzyme invertase can exist in two forms, depending on whether there is hydrolysis of

sucrose at the glucoside or fructoside linkage. In view of the results obtained in this study it is possible to postulate indirectly that *Neurospora crassa* is capable of producing both forms of the enzyme, depending on the sugar present in the medium. This view is based on (1) the difference in optimum pH for enzyme formation when grown on glucose or levulose, and (2) on the difference in the enzyme concentration per unit dry weight in the mycelia grown on the two sugars. In seeking an explanation for the two forms of invertase formed by growth on glucose or levulose, the theory proposed by Hinschelwood (26) was considered. As a mode of formation of adaptive enzymes, Hinschelwood proposed that the structure of the substrate influences the enzyme systems involved in assimilation. As the substrate is utilized, specific groupings (or special energy configurations) are incorporated into the cellular components. The enzymes thus asume new characteristics. When *Neurospora* is grown on a glucose containing medium, the invertase formed may be an α-glucosidase with an optimum pH of formation at pH 7.5. If levulose is substituted in the medium the enzyme, produced at an optimum pH of 6.0 to 6.5, will act on the fructoside linkage in sucrose. However, when the specific substrate, sucrose, is used in the growth medium, it is possible to follow the conversion of the α-glucosidase to fructo-invertase. The sucrose is first hydrolysed to glucose and levulose by the organism. Glucose, being preferentially utilized, gives rise to the α-glucosidase, with its characteristic optimum pH of formation. As glucose becomes exhausted, the levulose is attacked, and the nature of the enzyme changes, gradually becoming a fructosidase. Although the site of action differs, the two forms of the enzyme show the same optimum pH for invertase activity. The amount of enzyme formed, per unit mycelium, is much greater when the organism is grown on levulose than on glucose. This can be due to a natural tendency of the organism to produce fructosidase. The highly stimulatory effect of maltose on invertase formation is anomalous in view of the results obtained with glucose. Weidenhagen (27) has proposed a theory, since refuted by many investigators (28, 29), that the hydrolysis of maltose and sucrose were due to one and the same α-glucosidase. *Neurospora* is known to form a very active α-glucosidase (maltase) from maltose (10). Whether any relationship exists between maltase and the α-glucosidic invertase was not determined.

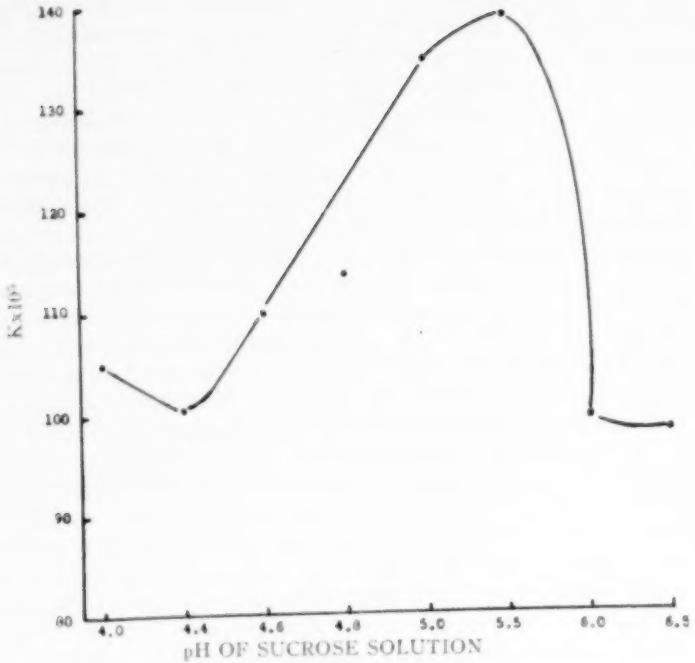

FIG. 2. pH-ACTIVITY CURVE FOR *N. Crassa* INVERTASE PRESENTING THE OPTIMUM pH RANGE FOR MAXIMUM INVERTASE ACTIVITY.

Summary and Conclusions

1. The effect of external environment and the chemical composition of the medium on the formation of invertase by *Neurospora crassa* was studied, especially the effects of the pH of the growth medium, age of organism, and carbon and nitrogen source.

2. The carbon compounds studied included glucose, levulose, sucrose, raffinose, xylose, maltose, mannose, lactose, galactose, arabinose, inulin, mannitol, sorbitol, dulcitol, succinate, malate, formate, tartrate, and saccharic acid salts.

The optimum pH for invertase formation by *Neurospora* when grown on glucose is between pH 7.0 and 7.5. On levulose the optimum pH lies between pH 6.0 and pH 6.5. Maximum invertase for-

mation occurred on the 5th day in both instances. With sucrose, maximum invertase formation occurred on the 3rd day at pH 7.0 to 7.5, changing by the 7th day to pH 6.0 to 6.5.

3. Invertase production was obtained when mycelia were grown in media containing raffinose, xylose and maltose. The other sugars listed above either did not support growth, or the mycelial formation was so diffuse that invertase activity could not be determined.

4. Media containing 2% glucose, levulose or sucrose yielded mycelia with greater invertase activity than other sugar concentrations.

5. The optimum pH range for invertase activity is between pH 5.0 and 5.5.

6. The nitrogen-containing compounds investigated included ammonium nitrate, ammonium tartrate, ammonium sulfate, monobasic ammonium phosphate, potassium nitrate, sodium nitrate, glycine, urea, casein hydrolysate, peptone and yeast extract.

Ammonium nitrate (2 mg. per ml.), ammonium tartrate (2 mg. per ml.), and urea (5 mg. per ml.) gave maximum invertase formation.

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BOOK REVIEW

Fundamentals of Pharmacy, 2nd Edition, Revised. By Walter H. Blome and Charles H. Stocking, 312 pages, 158 illustrations. Lea & Febiger, Philadelphia. $5.00.

The authors have divided this book into two distinct parts, titled respectively Theoretical Pharmacy and Practical Pharmacy.

Part I, the Theoretical Pharmacy section, covers the material usualy presented in the orientation course given most students commencing the study of pharmacy. Here, in twelve chapters, is discussed the nature of the various processes and equipment with which pharmacy is concerned. The mere mention of typical chapter titles, Specific Gravity, Comminution, and Extraction, will ring familiarly to all who have been exposed to such a course and illustrate the nature of the material presented.

In Part II, the Practical Pharmacy portion, most of the twenty-four chapters each discuss a particular type of pharmaceutical preparation. For example, there are chapters on Syrups, Tinctures, Suppositories and Tablets. Some of the later chapters of this section concern themselves with some of pharmacy's special fields such as Biological Products, Homeopathic Pharmacy and Hospital Pharmacy.

This entire book is characterized by a style of writing that is easy to read and understand, a credit to any book, especially to one primarly intended for the beginner. It is well illustrated, and the comment of the preceding sentence applies here too. Almost every subject presented is accompained by considerable historical data, more indeed than this reviewer has seen in any comparable volume.

Fundamentals of Pharmacy should prove useful both as a text and as a source of supplementary reading material to those who are beginning their studies in this field.

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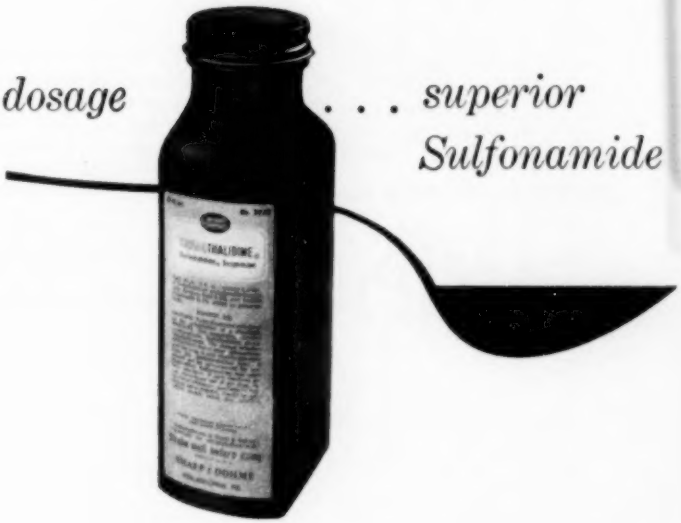

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